Contains Nonbinding Recommendations

Draft Guidance on Lidocaine

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

Active ingredient: Lidocaine

Form/Route: Patch/Topical

Recommended studies: 2 studies

1. Type of study: Fasting
   Design: Single-dose, *in-vivo*, using three topical patches
   Strength: 5%; 700 mg/ patch
   Subjects: Normal healthy males and females, general population.
   Additional Comments:
   - Apply three topical patches (2100 mg total dose) simultaneously over a 12-hour period.
   - You may use a smaller number of patches provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence assessment based on the 90% confidence interval criteria.
   - Please include a 24-hour post-dose sampling time in the bioequivalence study.
   - In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. The amount of adhesive residue from each patch left on the skin should be analyzed and included in the calculation.

Analytes to measure: Lidocaine in plasma.

Please utilize a validated analytical method such as LC-MS/MS to reliably measure plasma lidocaine concentrations. A lower limit of quantitation (LLOQ) of 0.20 ng/ mL is recommended to adequately characterize the pharmacokinetics at the 2100 mg study dose.

Bioequivalence based on (90% CI): Lidocaine

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2. Type of study: Skin irritation/sensitization study
   Design: Single-dose, *in-vivo* (preceded by an induction phase and a rest period)
   Strength: 5%; 700 mg/ patch
   Subjects: Normal healthy males and females, general population.
   Additional comments: Specific recommendations are provided below for the skin irritation/sensitization/adhesion study

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General comments:

- Please note that the name of RLD is designated as lidocaine topical patch, 5%. This designation is based on the concentration of lidocaine in the adhesive, which is 5%. Please formulate your product to contain 5% of lidocaine in the adhesive, to have the same surface area and the same total amount of lidocaine in the patch as the RLD.

- You may submit a full bioequivalence study protocol for review prior to initiating the study.

Waiver request of in-vivo testing: Not Applicable

Dissolution test method and sampling times:

Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.fda.gov/cder/ogd/index.htm. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

General recommendations regarding skin irritation/sensitization/adhesion evaluation of a generic lidocaine topical patch:

1. This product is intended to provide local pain relief of post-herpetic neuralgia at the application site. The RLD labeling directs that the patch should be cut to the appropriate size for the intended skin area to be treated. Therefore, your patch design must allow for the patch to be safely cut to a smaller size. In addition the active surface area of your patch should be comparable to that of the RLD.

2. Conduct the skin irritation and sensitization studies in healthy volunteers. Continuous same-site exposure is necessary to provide the maximal provocative exposure that is intended in the skin irritation and sensitization studies.

3. The clinical review team recommends that irritation and sensitization be evaluated in the same study. However, they should be evaluated with separate analyses. Primary endpoint(s) for each of these analyses need to be clearly defined prior to the start of the study. The two primary endpoints should be considered as co-primary endpoints, e.g., for each of them, the study must demonstrate that the test patches are no worse than the reference listed drug (RLD). In addition, the corresponding primary analysis for each primary endpoint needs to be specified in your protocol. Secondary endpoint(s) (if any) should also be clearly defined prior to the start of the study.

4. The OGD recommends that your patch have a design that can be cut to a smaller size as described in the labeling of the RLD. One-fourth of a test patch and one-fourth of the reference patch should be applied to the same individuals simultaneously for 21 days during the induction phase of the study. The patches should be applied continuously to the same sites and replaced with a new one-fourth patch 3 times weekly. The 21-day induction phase is to be followed by a 2-week rest period and then a single 48- hour challenge application of each one-fourth test system to a naïve site.

5. No make-up, creams, lotions, powders or other topical products should be applied to the skin area where the patch will be placed, as this could affect adhesive performance or induction of irritation.

6. Subjects should return for visits three times per week for irritation scoring and patch replacement during the induction phase. Scoring of skin reactions should be performed by a trained and blinded observer at each patch removal, using an appropriate scale. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. An example of an appropriate irritation scale is as follows:

   DERMAL RESPONSE

   0 = no evidence of irritation
   1 = minimal erythema, barely perceptible
   2 = definite erythema, readily visible; minimal edema or minimal papular response
   3 = erythema and papules
   4 = definite edema
   5 = erythema, edema and papules
   6 = vesicular eruption

7 = strong reaction spreading beyond application site

OTHER EFFECTS

0 = no other observations
1 = slight glazed appearance
2 = marked glazed appearance
3 = glazing with peeling and cracking
4 = glazing with fissures
5 = film of dried serous exudates covering all or part of the patch site
6 = small petechial erosions and/or scabs

7. If the degree of irritation for a given patch is such that a new patch cannot be applied to the same site, then the product should be discontinued and the highest score observed prior to patch discontinuation should be carried forward for all remaining observations in the irritation analysis. Subsequent applications of the product may be applied to a different skin site in order to complete the induction phase for the skin sensitization evaluation.

8. To be valid for cumulative irritation analysis, the sequential patch applications for the particular product must not be detached from the skin for longer than 24 hours during the 21 day induction period (unless the patch was removed for an unacceptable degree of irritation).

9. Scoring of skin irritation should not be limited to reactions that appear to be related to only one component of the generic system. Any skin reaction should be included in the irritation analysis, regardless of the area of the patch associated with the reaction.

10. The cumulative irritation score, the total number of observations with a maximum irritation score for each product, the number of patches that were removed due to an unacceptable degree of irritation, and the number of days until sufficient irritation occurred to preclude patch application should be calculated for each test and reference product, and a statistical analysis of the comparative results should be performed. In addition to the cumulative irritation scores, please provide a frequency chart showing the number of applications of each product with each irritation score on each study day. To support approval, the test product must be no more irritating than the reference product.

11. Subjects should be questioned about any itching, burning, pain or soreness at the application site. These symptoms should be recorded and compared between products.

12. To be included in the sensitization analysis, patches should be evaluated by a trained and blinded observer at 30 minutes, and at 24, 48 and 72 hours after removal of the challenge patch. Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of sensitization.

13. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of a contact sensitization. Your protocol will need to include a clear objective definition of a sensitization reaction *a priori*. The test product should be no worse than the reference product with regard to the rate of sensitization.

14. If a patch completely detaches, it should be replaced within 24 hours and the subject should continue in the study. If a patch cannot be replaced within 24 hours or a subject does not know when the patch fell off, the subject should be excluded from both the irritation and sensitization analyses of that product. The subject should note the date and time of detachment as soon as it occurs.

15. If you are not relying upon adhesion data from the skin irritation and sensitization study to establish adequate adhesion performance of your product, then you may consider establishing criteria for using

tape to reinforce any patches that are lifting during the study. In addition, you should consider replacing any detached patches within 24 hours to ensure valid cumulative irritation and sensitization induction.

16. Adhesion data should be collected during the course of the study to document that adhesion of the products is adequate for the intended induction of skin irritation and sensitization, even if you are not relying upon this study to establish adequate adhesive performance of your product.

17. Cutting patches to a smaller size is likely to change the shape as well as the size of the patch and may change adhesive performance of the patch. Therefore, adhesion data from your skin irritation and sensitization study may not be adequate to demonstrate that your to-be-marketed patch adheres at least as well as the RLD. Therefore, you should consider collecting adhesion data during your PK bioequivalence study, using an acceptable 5-point (0 to 4) scale. Reinforcement of the patches should therefore not be allowed in the PK study if it is also being used to demonstrate adequate adhesion, and you may need to increase the size of that study to allow for detached patches. Alternately, you may conduct a separate paired single-application adhesion study to demonstrate that your product adheres at least as well as the RLD.

18. For adhesion analysis, please provide adhesion scores for a single application of the intended duration of patch wear using a scale such as the following:

    0 = ≥ 90% adhered (essentially no lift off of the skin)
    1 = ≥ 75% to < 90% adhered (some edges only lifting off of the skin)
    2 = ≥ 50% to < 75% adhered (less than half of the system lifting off of the skin)
    3 = < 50% adhered by not detached (more than half the system lifting off of the skin without falling off)
    4 = patch detached (patch completely off the skin)
    For any patch that detaches, please carry forward a score consistent with detachment for all remaining observation periods.

19. The cumulative adhesion score and the time from application until patch detachment should be calculated for each test and reference product, and a statistical analysis of the comparative results should be performed. In addition to the mean cumulative adhesion scores, please provide a frequency chart showing the number of patches in each group with each adhesion score at each observation. Please also provide data regarding the number of patches that detached and duration of wear prior to detachment. To support product approval, the test product must adhere at least as well as the reference product.

20. Due to likely differences in appearance of the patches, blinding of the observer/evaluator may not be possible, especially for evaluation of patch adhesion, which requires direct observation of the patch itself. However, efforts should be made to blind the evaluation of irritation and sensitization.

21. The same investigator should perform all irritation evaluations and/or all patch adherence evaluations for each individual subject. The sponsor should consider training all investigators and potential alternates according to the protocol in order to ensure consistency in evaluations.

22. The study results should show that the proposed product does not produce any greater degree of irritation or sensitization than that produced by the RLD and that the adhesive performance over the intended duration of wear is at least as good as that of the RLD.

23. The analysis populations should be defined separately for irritation and sensitization and should be defined per product instead of per subject. Each property should have a separate test population and reference population for each product.

24. The Population Definitions for the Per-Protocol (PP) evaluation for each parameter should include the following:

- Irritation Analysis– a product needs to be worn for the entire 3 weeks to be valid for the cumulative irritation evaluation OR if a patch is removed due to excessive irritation, it should be included using Last Observation Carried Forward (LOCF).
- Sensitization Analysis – all subjects that wear the product for the full 21 day induction phase and for 48 hours during the challenge phase and return for evaluation 24 hours after removal of the challenge patch (OR if the product is removed prior to 48 hours due to a sensitization reaction that caused the product to be removed) should be included using LOCF.

25. As the irritation and adhesive properties may be sensitive to climate changes, we prefer that the study be conducted in multiple centers with varying climate conditions

26. Please refer to 21 CFR 320.38 and 320.63 regarding retention of study drug samples. For more information, please refer to the Guidance for Industry: "Handling and Retention of BA and BE Testing Samples" (May 2004). Retention samples should be randomly selected from each drug shipment by each study site prior to dispensing the medication to subjects. Samples must be randomly selected at each investigational site where the medication is dispensed and retained by the investigator or an independent third party not involved with packaging and labeling of the study products. Retention samples should not be returned to the sponsor at any time.

27. It is recommended that an independent party generates and holds the randomization code throughout the study in order to decrease the chance of unblinding and to minimize bias. The sponsor may generate the randomization code if not involved in packaging and labeling of study drugs.

28. A sealed copy of the randomization scheme should be retained at the study site and should be available to FDA investigators at the time of site inspection to allow verification of the treatment identity for each subject.

29. The OGD generally does not provide sample size recommendations. It is your responsibility to include sufficient patients in the study to demonstrate non-inferiority of skin irritation potential and adhesion performance of your product compared to the reference listed drug (RLD).

30. When submitting results of skin irritation, sensitization and adhesion studies in an ANDA, study data should be submitted in electronic format including the following information:
    a. A list of file names included in the CD or diskette(s) with a simple description of the content of each file. A document file containing a description of each dataset and an explanation of the variables included in each of the SAS datasets. (See http://www.fda.gov/cder/guidance/2353fnl.pdf regarding "define.pdf.")

        All SAS transport files should use .xpt as the file extension and should not be compressed. The SAS program to open the transport files and an explanation of the format for each SAS variable should be included.

    b. You should identify and provide the list of subjects that are included and excluded from each population analysis separately for each product. The variable(s) derived for analysis should include specific data such as treatment per patch, analysis populations (e.g., per protocol (PP) for each of the three analyses), irritation scores, days to patch detachment, days to patch removal, etc. You should also provide the reason(s) for exclusion of subjects from each of the PP and other population(s) used for analysis. These variables could be included in a single SAS transport file.

    c. SAS transport file(s) – covering all variables collected in the Case Report Forms (CRFs) per subject: You should provide a summary dataset to include such variables as demographics, baseline admission criteria, baseline vital signs, adverse events, reasons for discontinuation of treatment, medical history, compliance and comments, etc.

Primary data sets should consist of two data sets: No Last Observation Carried Forward (No-LOCF-pure data set) and Last Observation Carried Forward (LOCF-modified data set).

d. The methods used to derive the variables should be included and explained.

e. The following line listings should be provided for each subject:

- Center/site, subject number
- Race, sex, age
- Adverse events, reason for discontinuation
- Analysis populations for each patch:
  - Test product PP population for irritation analysis (yes/no), reason for exclusion
  - Reference product PP population for irritation analysis (yes/no), reason for exclusion
  - Test product PP population for sensitization analysis (yes/no), reason for exclusion
  - Reference product PP population for sensitization analysis (yes/no), reason for exclusion
  - Test product PP population for adhesion analysis (yes/no), reason for exclusion
  - Reference product PP population for adhesion analysis (yes/no), reason for exclusion

- Patch removed due to strong skin irritation reaction (yes/no)
- Time from first patch application to removal for unacceptable irritation
- Cumulative number of patches removed for unacceptable irritation
- Cumulative number of detached patches
- Reinforced with tape (yes/no)
- Number of days until reinforcement with tape
- New patch application due to detachment (yes/no)
- Date of a new patch application due to detachment
- Time from application to detachment
- Designation of skin sensitization (yes/no)
- Per each visit if data exist
  - Visit number, date of visit, days from baseline
  - Reason for exclusion from each PP population per visit
  - Time from patch application to detachment for both test and reference products
  - Irritation scores for each product
  - Sensitization scores for each product
  - Adhesion scores for each product
  - Identity of the evaluator
  - adverse events
  - reason for discontinuation

31. The OGD is currently evaluating the appropriate statistical tests that should be used to analyze clinically meaningful differences between products with regard to skin irritation, sensitization and adhesion.

32. Please note that the guidance provided in this letter supersedes information provided in the *Guidance for Industry: Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products*, which has been withdrawn and is currently under revision.

33. Please be advised that the information given in this letter is general in nature and represents the current thinking of the Clinical Review Team and the Office of Generic Drugs. The OGD recommends that you submit protocols to the Clinical Review Team for review and comment prior to conducting the studies.